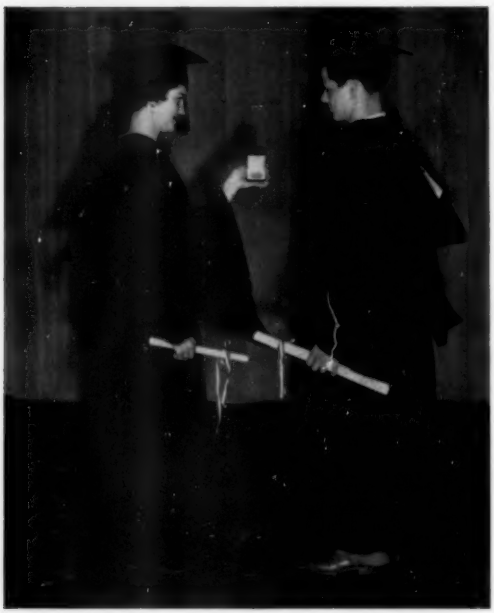
AMERICAN Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH



THE PHARMACY GRADUATE—
OPPORTUNITIES UNLIMITED

Since 1825 *May 1957*

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription $4.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 40 Cents — Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879

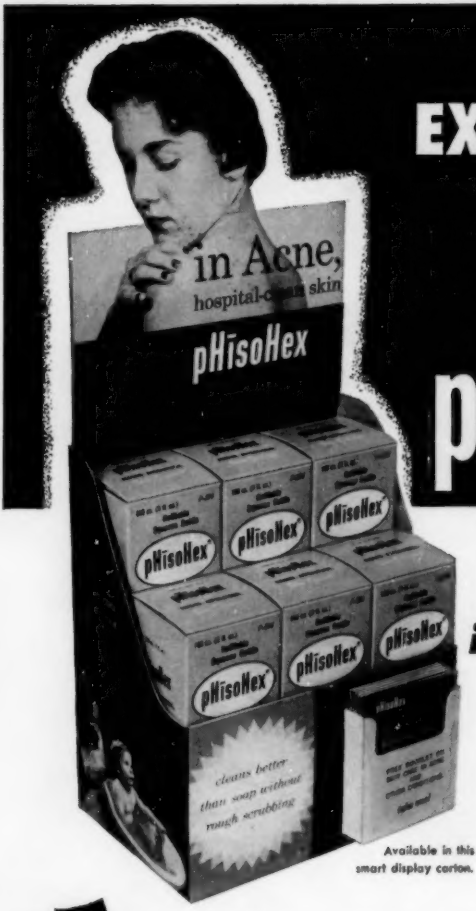
a good habit to maintain **GERIPLEX®** KAPSEALS®

one day out of stock may change buying habits that have endured for years...

keep well supplied with **GERIPLEX KAPSEALS**, available in bottles of 100 and 500.

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

EXTRA PROFITS FOR YOU ON pHisoHex®



Available in this smart display carton.

SUDSING • ANTIBACTERIAL SKIN CLEANSER

in 2 BIG FREE GOODS DEALS

HEAVILY PRESCRIBED FOR "HOSPITAL CLEAN" SKIN IN HOME PATIENT CARE

1

		Cost	Sell
YOU BUY	11 5 oz. pHisoHex @ $1.07	$11.77	$17.60
YOU GET	1 5 oz. pHisoHex	FREE	1.60
	YOUR PROFIT $7.43 or 39%	$11.77	$19.20

2

		Cost	Sell
YOU BUY	11 16 oz. pHisoHex @ $1.70	$18.70	$28.16
YOU GET	1 16 oz. pHisoHex	FREE	2.56
	YOUR PROFIT $12.02 or 39%	$18.70	$30.72

ACNE:
Massage of pHisoHex suds into the skin three times a day followed by thorough rinsing is a valuable adjunct in acne treatment.

DIAPER RASH:
Regular bathing of the baby with pHisoHex helps to prevent diaper rash and other skin irritations.

IMPETIGO:
Skin infections in babies and children can be prevented by washing regularly with pHisoHex. Mothers and others handling the baby should also wash their hands with pHisoHex.

pHisoHex, trademark reg. U. S. Pat. Off.

Order full stocks today through your wholesaler or Winthrop representative.

Winthrop LABORATORIES
1450 BROADWAY | NEW YORK 18, N. Y.

AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

Vol. 129 MAY 1957 No. 5

CONTENTS

E D I T O R I A L

OPPORTUNITIES FOR THE PHARMACY GRADUATE

THE opportunities available for the graduates this year of our seventy-six colleges of pharmacy in the United States were never better. Few, if any, of those students graduating have failed to receive several excellent offers of employment, and many fields of pharmaceutical endeavor are open to those who seek some type of employment other than in retail pharmacy. The extent and variety of these employment offers is a healthy sign, as viewed on one side of the picture, and a cause of concern by those on the other who are prospective employers rather than employees. As with many things, the interests of all parties concerned are best served when the supply of pharmacists never quite meets the demand but, at the same time, does not fall too far short of it.

From a strictly objective viewpoint, few fields offer the opportunity provided by a training in pharmacy. Viewed from the economic standpoint, only graduate engineers are paid more in their starting salary than is the young graduate in pharmacy. Statistics will show, however, that on the average the pharmacist after ten years, particularly if he operates his own establishment, earns more than the average engineer working for industry. While the operation of a retail pharmacy may on the surface lack some of the glamour of other positions in the field, such as medical detailing, pharmaceutical research, teaching, etc., it still offers the greatest opportunity of all for community service and economic reward. If retail pharmacists themselves were less inclined to complain about the vicissitudes of retail practice, more young people undoubtedly would choose this field for, in the long run, it would be to their advantage.

One hears today, particularly from retail pharmacists, about the crying need for pharmacists and there does seem to be a deficiency of pharmacists to man the existing number of drugstores. Whether there are more stores than are needed or even more stores than serve the best interests of the public and the profession is a matter of opinion, and there are some very sincere and well-meaning persons who feel that there are too many.

The shortage of pharmaceutical personnel, while it has brought certain hardships, particularly on store owners, has also resulted in a number of changes for the better. Salaries now paid employee-pharmacists are much more realistic, today, and more in keeping with their qualifications as professionally trained persons. This in turn has caused employer-pharmacists to look more critically at what must be charged for professional service in the operation of the pharmacy itself. Far too many in the past totally ignored this cost which surely is one which can be justified if, indeed, the pharmacist is more than an ordinary merchant.

Pharmacists in practice should not be too much disturbed over the relative shortage of pharmacists for, if there were an oversupply, the economic position of all would be seriously impaired. Those who would do something to improve the supply of pharmacists would do well in trying to interest intelligent and capable young men and women in the profession. The pharmacist who presents in his community the picture of an unhappy, overworked, and utterly miserable person is not likely to influence the proper kind of young person to follow in his footsteps. While we cannot change the attitude and appearance of some few individual pharmacists, we can point quite unmistakably to the many golden opportunities for service and reward which a young man or a young woman will find waiting after preparation in college.

L. F. Tice

COMPARATIVE EFFICIENCY OF VARIOUS EMULSIFYING AGENTS USING DIFFERENT EQUIPMENT*

By Josephine M. Siragusa,** William J. Husa and Charles H. Becker

Emulsions were made from four oils stabilized with gum and nonionic emulsifiers. Different emulsification machines were employed. Results indicate that acacia was the most efficient emulsifier; the best results were obtained using the two-stage homogenizer. The blender or hand homogenizer was more suitable for the practicing pharmacist and gave satisfactory results. Castor oil seemed the easiest to emulsify; mineral oil was next to castor oil in ease of emulsification. Mixtures of emulsifying agents showed little or no advantage over acacia alone as the emulsifier.

THE need for emulsion stability is great since this class of pharmaceutical preparations is one of the best ways to administer oils both orally and parenterally.

Extensive investigations of different emulsifiers as well as different manufacturing procedures have been carried out and reported in the journals by King (1), Munzel (2), Husa and Becker (3) and Lotzkar and Maclay (4). However, it is difficult to interpret many of these results since the procedures and testing methods differ vastly from one another.

The present investigation was undertaken with the view in mind of making a comparative study of some of the emulsifiers generally used in pharmacy and mixtures of some of these, employing several different emulsifying machines to make the emulsions.

---

* Abstracted from a dissertation submitted by Josephine M. Siragusa to the Graduate Council of the University of Florida as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

** Fellow of the American Foundation for Pharmaceutical Education. Present address: Loyola University, College of Pharmacy, New Orleans, Louisiana.

The authors wish to express their gratitude to Kelco Company for the Kelgin® and S. B. Penick and Company for the acacia and tragacanth used in this investigation.

TABLE 1

CONCENTRATION OF EMULSIFIERS USED

Emulsifier	Concentration in Per Cent
Acacia	3.13 w/v
Tragacanth	0.32 w/v
Kelgin®	1.00 w/v
Span®-Tween® blend	1.00 v/v
Mixture 1	2.82 w/v acacia
	0.10 w/v Kelgin®
Mixture 2	0.31 w/v acacia
	0.90 w/v Kelgin®
Mixture 3	2.82 w/v acacia
	0.03 w/v tragacanth
Mixture 4	0.31 w/v acacia
	0.29 w/v tragacanth
Mixture 5	2.82 w/v acacia
	0.10 v/v Span®-Tween® blend
Mixture 6	0.31 w/v acacia
	0.90 v/v Span®-Tween® blend
Mixture 7	0.90 v/v Span®-Tween® blend
	0.03 w/v tragacanth
Mixture 8	0.10 v/v Span®-Tween® blend
	0.29 w/v tragacanth

Experimental

Materials Used—The four oils selected for use in this investigation were castor oil, cod liver oil, linseed oil and mineral oil; the oils were of U. S. P. or N. F. quality. In all cases 12½ per cent v/v oil emulsions were prepared.

Acacia, tragacanth, Kelgin®, a blend of Span® 20 and Tween® 80, and mixtures of these emulsifiers were selected for use in this work. Table 1 shows the concentration of emulsifiers and mixtures of emulsifiers used in the preparation of the emulsions.

Span® 20 and Tween® 80 have been assigned HLB numbers 8.6 and 15.0 respectively (5). A mixture of 85 per cent v/v Span® 20 with 15 per cent v/v Tween® 80, having a calculated HLB value of 9.6, was used throughout these experiments.

Kelgin® supplied by the Kelco Company.

Span® 20 and Tween® 80 supplied by the Atlas Powder Company.

The following equipment was used in the preparation of the emulsions:

(a) a No. 1 wedgwood mortar and pestle;

(b) a cast aluminum hand homogenizer with stainless steel and chromium plated orifice and piston parts;

(c) a model 10 Osterizer blender manufactured by the John Oster Manufacturing Company, Racine, Wisconsin;

(d) an Eppenbach colloid mill, QV6 type, manufactured by the Admiral Tool and Die Company, Inc., Long Island City, New York;

(e) a Manton-Gaulin two-stage homogenizer, Model B, manufactured by the Manton-Gaulin Manufacturing Company, Inc., Everett, Mass.

General Methods—In this work "primary emulsion" means the emulsion which resulted when the oil, emulsifiers and a portion of the distilled water were triturated together. The primary emulsion was considered successful if it gave a clicking sound when triturated, was creamy, opaque and showed no oil separation. The quantity of water used to prepare the primary emulsion was 6.25 per cent v/v of the total emulsion, with the exception of Kelgin®, when 25 per cent v/v water was added, and with Span®-Tween® blend, when the entire quantity of water was added.

The emulsions were prepared by the following general methods:

(a) Mortar and Pestle Method—Sixty cc. portions of the emulsions were prepared in each case by the Continental method. The oil and emulsifier were triturated in the mortar for approximately a half minute, the distilled water added and the primary emulsion triturated for five minutes before diluting to 60 cc. The mortar and pestle method was not employed when using the Span®-Tween® emulsifier blend. Instead, the oil and emulsifier were mixed in a bottle and sufficient distilled water added to make the product measure 60 cc. The preparation was shaken for five minutes.

(b) Hand Homogenizer Method—Sixty cc. portions of the emulsions were prepared in each case. The oil and emulsifier were triturated in a wedgwood mortar for approximately a half minute

before diluting to 60 cc. The emulsion was then passed through a hand homogenizer three times. However, in the case of the Span®-Tween® blend, the emulsifier was mixed with the oil in a beaker and enough distilled water added to make the product measure 60 cc. The system was stirred with a stirring rod for approximately a half minute before passing it three times through the hand homogenizer.

(c) Blender Method—Two hundred forty cc. portions of emulsions were prepared. The water and emulsifier were blended in the Osterizer and then the oil added. The mixture was agitated for five minutes and diluted to 240 cc. with constant stirring. This procedure was employed to prepare emulsions except in the cases of Kelgin® and Span®-Tween® blend. In the Kelgin® emulsions, the Kelgin® was mixed with the oil, distilled water added and the mixture agitated for five minutes before diluting to 240 cc. The Span®-Tween® blend was also mixed with the oil in the Osterizer before emulsification.

(d) Colloid Mill Method—Five hundred cc. portions of emulsions were prepared. The water and emulsifier were stirred in a beaker, the oil added and the mixture diluted to 500 cc. with distilled water. The mixture was passed twice through the Eppenbach colloid mill, re-cycled for five minutes and collected. The micrometer arrangement regulating the gap between the rotor and stator was set at 20 in the preparation of all the emulsions. Kelgin® and Span®-Tween® blend were mixed with the oil, the distilled water added, and emulsification carried out in the same manner as with the other emulsifiers.

(e) Two-Stage Homogenizer Method—Five hundred cc. portions of emulsions were prepared. The water and emulsifier were stirred well in a beaker, the oil added and then sufficient water was added to make the product measure 500 cc. The mixture was passed three times through the Manton-Gaulin two-stage homogenizer at 1500 pounds pressure per square inch on the first valve and the second valve set at a pressure of 1000 pounds per square inch. In the case of the Kelgin® and the Span®-Tween® blend emulsions, these emulsifiers were first mixed thoroughly with the oil before diluting to 500 cc. Then they were passed through the homogenizer.

TABLE 2

SUMMARY OF EMULSIONS PREPARED WITH SINGLE EMULSIFIERS

Emulsifiers	Oils		Equipment: Mortar and Pestle c	Mortar and Pestle d	Hand Homogenizer c	Hand Homogenizer d	Blender c	Blender d	Colloid Mill c	Colloid Mill d	Two-stage Homogenizer c	Two-stage Homogenizer d
Acacia		a	B		B		A		B		A	
	Castor oil	b	B*	B*	C*	C*	B*	C*	C*	C*	B*	B*
		a	B		B		A		B		A	
	Cod liver oil	b	C*	B*	C*	C*	B*	B*	C*	C*	B	B
		a	C		C		A		B		A	
	Linseed oil	b	B*	B*	C*	C*	B*	B*	B*	C*	A	B
		a	C		C		B		B		B	
	Mineral oil	b	C*	C*	C*	D*	B*	C*	D*	D*	B*	B*
Tragacanth		a	B		B		B		D		B	
	Castor oil	b	D*	D*	C	C	C*	B*	D	C	B*	B*
		a	D		C		D		D		B	
	Cod liver oil	b	D″	D″	D″	D″	D*	D*	D	D″	C*	D″
		a	C		B		B		C		B	
	Linseed oil	b	D″	D″	C*	C*	C*	D*	C	C	B	B
		a	C		C		D		D		C	
	Mineral oil	b	D″	D″	D*	D*	D*	D*	D	D*	C*	C*
Kelgin®		a	C		B		B		B		B	
	Castor oil	b	D*	D*	D*	D*	C*	D*	B*	D*	C*	D*
		a	D		D		B		C		B	
	Cod liver oil	b	D*	D″	D*	D*	D″	D*	D*	D″	C*	D″
		a	D		C		C		C		B	
	Linseed oil	b	D*	D″	C*	C″	B*	B*	B*	B*	B*	C*
		a	D		C		C		C		D	
	Mineral oil	b	D″	D″	D*	D*	D*	D*	D*	D*	D*	C*
Span®-Tween® Blend		a	D		D		B		C		B	
	Castor oil	b	D*	D*	C*	C*	D″	C″	C″	C″	B*	C*
		a	D		B		B		B		A	
	Cod liver oil	b	D″	D″	B*	C″	C″	C″	B*	C″	A*	A*
		a	C		B		C		B		A	
	Linseed oil	b	D″	D″	C″	C″	C″	C″	C″	C″	A	A
		a	C		B		B		A		A	
	Mineral oil	b	C*	C*	B*	C*	B*	B*	C*	C″	A*	A*

a—immediately

b—one month storage

c—storage at room temperature

d—storage at 37° C.

*—creamed

″—oil separation

In order to assure uniformity, the pressure settings were obtained by adjusting the machine on water. When the desired pressure had been reached and the homogenizer was operating smoothly, the water was diverted to a suitable container. When the water had nearly disappeared from the intake pipe, the emulsion mixture was added. This method of adjusting the pressure on water assured uniform homogenization of the entire system. A small portion of the initial homogenized product was discarded, as it was practically all water. Three separate homogenization passes were used, rinsing the machine well between passes and building the pressures as described above. It was felt that the use of three passes assured triple exposure of the entire emulsion to the hydraulic shear of homogenization to a greater extent than would re-cycling for a standard period of time.

Storage of Emulsions—Emulsion samples were stored in clear glass screw-capped prescription type bottles. Emulsions made by the mortar and pestle and the hand homogenizer methods were stored in one ounce bottles having a capacity of two ounces. Samples were stored at room temperature and in an electric oven at 37° C. Before analysis each sample was shaken gently to redistribute any creamed portion of the emulsion.

Determination of Quality—The quality of the emulsion was determined by making microscopic measurements of the size of the *dispersed* globules immediately after emulsification and after standing for a period of one month both at room temperature and at 37° C. by the method outlined by Husa and Becker (6). The appearance of the emulsion and rate of creaming and oil separation were also observed.

In the tables "oil sep." is used to indicate oil separation; where the phrase "no change" appears, it signifies that no visible creaming occurred during the one month storage period. The following abbreviations are used to indicate the average size of the oil globules:

A—average diameter less than 2.5 microns

B—average diameter from 2.5 to 4 microns

C—average diameter from 4 to 6 microns

D—average diameter more than 6 microns

TABLE 3

LINSEED OIL EMULSIONS USING MIXTURES OF EMULSIFIERS

Emulsifiers		Equipment Used			
		Mortar and Pestle		Two-Stage Homogenizer	
		a	b	a	b
Mixture 1	c	B	C Creamed	A	A No change
	d		C Creamed		A No change
Mixture 2	c	C	D Creamed	B	B Creamed
	d		D Creamed		B Creamed
Mixture 3	c	B	B Creamed	A	A No change
	d		C Creamed		A No change
Mixture 4	c	D	D Creamed	B	B Creamed
	d		D Creamed		B Creamed
Mixture 5	c	D	C Oil sep.	B	B Creamed
	d		D Oil sep.		B Creamed
Mixture 6	c	C	D Oil sep.	A	B Creamed
	d		D Oil sep.		B Creamed
Mixture 7	c	C	C Oil sep.	A	A Creamed
	d		C Oil sep.		A Creamed
Mixture 8	c	C	C Creamed	A	B Creamed
	d		D Creamed		B Creamed

a—immediately
b—one month storage
c—storage at room temperature
d—storage at 37° C.

Discussion

Emulsions Prepared with Acacia—The two-stage homogenizer prepared the best emulsion when emulsifying the four oils with acacia using the different methods. Cod liver and linseed oils appeared to be the oils best emulsified. No oil separated out in any of the emulsions prepared with acacia as the stabilizing agent.

Emulsions Prepared with Tragacanth—In general tragacanth did not produce very stable, white, creamy emulsions. They were coarse and some showed oil separation. The linseed oil emulsions made in the two-stage homogenizer and the castor oil, hand homogenized emulsion, were best in this group of emulsions.

Emulsions Prepared with Kelgin®—The majority of the emulsions prepared with Kelgin® were coarse and creamed. The oils best emulsified were castor oil and linseed oil made with the two-stage homogenizer, colloid mill, blender, and hand homogenizer. Oil separated in a large number of the emulsions and these were prepared employing the mortar and pestle, the two-stage homogenizer, the blender and the hand homogenizer.

Emulsions Prepared with Span®-Tween® Blend—The majority of the emulsions prepared with the Span®-Tween® blend as emulsifier showed oil separation. Each of the four oils gave at least one product that showed oil separation. Those showing oil separation were made in the colloid mill, blender, hand homogenizer and the mortar and pestle. None made employing the two-stage homogenizer showed oil separation.

Comparison of the Four Emulsifying Agents—Acacia was the best for emulsification of the four oils used. No oil separation appeared in the emulsions stabilized with acacia. As far as pharmaceutical emulsions are concerned, emulsions that cream are satisfactory since the creamed portion may be redistributed by shaking. Of course, the ideal situation would be an emulsion which would show no visible creaming.

Tragacanth and Kelgin® seemed to be almost equal in emulsification ability. This is probably due to the fact that both owe their emulsification ability mainly to the fact that they increase viscosity of

the preparation and thus aid in preventing coalescense of the oil globules. Some of the emulsions prepared with these emulsifying agents showed oil separation.

A majority of the emulsions prepared with the Span®-Tween® blend showed oil separation. The concentration of this emulsifying agent used in the experiments was apparently not high enough to produce satisfactory emulsions. The emulsions prepared did not appear as viscous as those prepared by the other three emulsifying agents.

Comparison of the Equipment Used—The majority of the emulsions prepared in the two-stage homogenizer were grade A and B, with only a small percentage showing oil separation. The blender was second best; the hand homogenizer and colloid mill seemed to be effective to approximately the same degree and occupy third place for efficiency; the mortar and pestle seemed to be the poorest.

The two-stage homogenizer, producing the best emulsions, would be most useful for the pharmaceutical manufacturer but would not be suitable for the practicing pharmacist due to the high cost and capacity. For the practicing pharmacist, the blender and the hand homogenizer have some advantages over the mortar and pestle. The blender takes less time for the preparation of the emulsion and less care is needed in its preparation. The blender does, however, incorporate a great deal of air into the preparation, which might be a disadvantage in certain cases. As contrasted to the blender, more time is consumed in cleaning the hand homogenizer than is spent by the ordinary pharmacist in the preparation of the volume of emulsions usually dispensed. Conditions must be just right and great skill is needed in order to produce satisfactory emulsions when employing the mortar and pestle.

Comparison of the Four Oils—Castor oil seemed the easiest to emulsify of the four oils. Mineral oil seemed to be the second easiest to emulsify. Both linseed and cod liver oils gave a high percentage of emulsions that showed oil separation. However, linseed oil gave the greatest percentage of grade A stable emulsions.

Mixed Emulsifying Agents—Inasmuch as linseed oil seemed to differ so widely in the results obtained, giving high percentage of grade A stable emulsions as well as a high percentage of those that

showed oil separation, it was decided to study this oil with mixtures of emulsifiers.

The equipment used in the investigation of these mixtures represented the equipment that gave the best results and the one most likely to be used by the manufacturers, the two-stage homogenizer, and the one that imparted the poorest stability, as well as the one used by the practicing pharmacist, the mortar and pestle.

Since acacia proved to be the best emulsifier it was decided to try mixtures in which a small percentage of the acacia was replaced with small proportion of the other emulsifying agents, represented by mixtures 1, 3 and 5. Other mixtures were tried in which a small percentage of the other emulsifiers, tragacanth, Kelgin® and Span®-Tween® blend, was replaced with a small proportion of acacia in order to observe whether this small percentage of acacia would improve the emulsification ability of the other emulsifiers. These are represented by mixtures 2, 4 and 6.

Inasmuch as Span®-Tween® blend did not possess high viscosity, a small percentage of tragacanth was used to replace part of the Span®-Tween® blend in mixture 7. This was done to see if a small percentage of a highly viscous substance might improve the stability of the Span®-Tween® blend emulsions. Mixture 8 was tried to see what the effect might be if a small percentage of Span®-Tween® blend replaced a portion of the tragacanth, a highly viscous substance.

Replacing a small part of acacia with other emulsifiers gave no improvement over the emulsions stabilized with acacia alone. In the case of the mixtures containing a small proportion of acacia replaced with a small percentage of Span®-Tween® blend, emulsions were obtained that were inferior to the ones produced when the Span®-Tween® blend was used alone as the emulsifier.

The replacement of a small percentage of the other emulsifiers with a small quantity of acacia gave varied results.

The addition of a small proportion of acacia to Kelgin® greatly improved the emulsion. The resulting preparation was almost as good as when acacia was used alone.

Replacing a small portion of tragacanth with acacia prevented oil separation that occurred when tragacanth alone was employed to prepare the emulsions in the mortar and pestle; however, there was no improvement in grade over emulsion stabilized with tragacanth alone.

No improvement was seen when a small proportion of Span®-Tween® blend was replaced with a small percentage of acacia. Also no improvement was noted when a small percentage of Span®-Tween® blend was replaced with a small proportion of tragacanth. However, when a small portion of tragacanth was replaced with a small percentage of Span®-Tween® blend, better emulsions resulted inasmuch as no oil separation occurred as was the case for the individual emulsifiers.

REFERENCES

(1) King, A. and Mukherjee, L. N., *J. Soc. Chem. Ind., 59,* 185 (1940).

(2) Munzel, K., *Pharm. Acta. Helv., 18,* 32 (1943).

(3) Husa, W. J. and Becker, C. H., *J. Am. Pharm. Assoc., Sci. Ed., 30,* 141 (1941).

(4) Lotzkar, H. and Maclay, W. D., *Ind. Eng. Chem., 35,* 1294 (1943).

(5) "Atlas Surface Active Agents," Industrial Chemical Department, Atlas Powder Company, Wilmington, Delaware (1950).

(6) Husa, W. J. and Becker, C. H., *J. Am. Pharm. Assoc., Sci. Ed., 30,* 83 (1941).

THE HOSPITAL PHARMACIST'S RESPONSIBILITIES IN THE PRODUCTION OF PARENTERALS *

By Louis Gershenfeld **

ONE hundred twenty-five years ago (to be exact in 1831), Thomas Latta of Scotland advised the intravenous administration of saline solutions in the treatment of cholera. The dramatic results afforded by such procedure in restoring quickly the fluid and salt balance of the body in these patients assured the use of this as a route for administering medicinals. In 1853, Alexander Ward introduced a method for the hypodermic administration of medicaments to be followed by Pravaz, who in the same year invented the hypodermic syringe. In 1886, Stanislas Limousin, the French chemist, devised at the suggestion of Dr. Duhomme, the sealed glass ampul practically as it is employed today.

I am sure you all know the many reasons for using the parenteral route. Briefly, the more important reasons are: rapidity of action; assurance of activity (as some medicaments are destroyed or are modified or rendered useless when given orally); assurance of potency, proper dosage and better control (due to poor or uncertain absorption from the intestinal tract); for the administration of drugs having a short duration of activity and a low margin of safety; and for patients, who cannot or will not swallow or who have gastrointestinal abnormalities or are comatose. The indiscriminate use of personalized medication by others for whom the original prescription was not intended is also eliminated in the administration of drugs by the parenteral route.

Preparation of Parenterals

Twenty-six years ago, or to be exact in June, 1931, I presented a paper before the Pennsylvania Pharmaceutical Association 54th annual meeting entitled: "Who is to Dispense Therapeutic Agents Intended for Hypodermic and Intravenous Injection"? It was published later that year (1).

---

* Presented at the Pre-Convention Conference of the American Society of Hospital Pharmacists on "Preparation of Parenteral Products by the Hospital Pharmacist" held in New York City on April 27, 1957.

** Director, Department of Bacteriology, Philadelphia College of Pharmacy and Science.

In April, 1933, I wrote an Editorial for the American Journal of Pharmacy concerning the need for the more careful control of regulating the proper labeling as well as the traffic in ready-made parenteral solutions (2). The following year, the Committee of Pharmacy and Chemistry of the American Medical Association, taking cognizance of this editorial, presented a four page report on the "Sterility of Ampoule Preparations," which begins with the statement "Following Gershenfeld's article a resurvey was started of these ampoule preparations" (3). Immediately thereafter, I was contacted by the Food and Drug Administration who then arranged for an extensive nation-wide inspection and testing program.

During these intervening years, much progress has been made in the field of parenteral manufacturing. Numerous articles have appeared by myself (4, 5) and others (6). I have always been concerned with the responsibility of the pharmacist in this phase of pharmaceutical practice. Unfortunately, a statement made by me more than a quarter of a century ago still applies: "Pharmacists display a laxity in taking advantage of their scientific training and in combining their aggressive and skillful merchandising ability for the benefit of professional pharmacy".

You may say that the above statement applies to pharmacists in the retail field. When the statement was originally made, it applied to pharmacists in all fields including, of course, Hospital Pharmacists. After all, the responsibility of compounding and dispensing medicinal agents in a hospital or elsewhere is the responsibility of a properly trained pharmacist. However, it must be recognized that the professional training, ability and experience of the hospital pharmacist will in great measure influence the kind and the extent of effective pharmaceutical service, including the production of parenterals, which can be and is rendered. The preparation of parenterals provides the widest scope for every talent possessed by a pharmacy graduate. An opportunity is presented here to perform an indispensable service and health function, which is bound to promote interprofessional relationships of the highest order and increase the prestige of professional pharmacy. However, it must be recognized at all times that in the manufacture of parenterals, the pharmacist must be qualified by training and experience to perform such duties. He must equip himself with the necessary facilities required, pay greater attention to detail than is practiced for the preparation of oral and other kinds of

medicaments, and surround himself with and constantly practice rigid control.

Chemicals in Parenteral Solutions

Chemicals only of the highest purity should be employed in the preparation of parenteral solutions and especially those to be used for intravenous administration. Where known quality grades have proven to yield constantly satisfactory preparations, it may be advisable to purchase only such high grade chemicals of known purity. Particulate matter such as dust, dirt, debris and even insect parts have been found in containers of various chemicals and especially in those holding bulk chemicals, such as dextrose, salt and sodium citrate. Portions of any chemical or drug, which drops on the balance or on the table should be discarded and not returned to the container. The use of dirty implements and scale pans should be avoided. The possibility of contamination with pyrogenic substances always exists.

Water for Injection

The procedure used to prepare a pyrogen-free water is of greatest importance. Suitable equipment is available which will provide a pyrogen-free distillate, but intelligent operation at all times even of a satisfactory still is essential. The storage vessel or container for the distillate must be scrupulously clean and properly protected to prevent contamination. If the empty storage vessel is not sterilized beforehand, it should be washed out with live steam or with several rinsings of pyrogen-free water before use. To prevent pyrogenic properties being imparted to the distillate, pyrogen-free water should be distributed in suitable containers and properly sealed and sterilized in their final containers immediately after distillation, unless such water is to be used at once for preparing solutions for parenteral use. However the finished solutions should be sterilized within one working day. If this is not practicable, the pyrogen-free water can be stored under refrigeration at a temperature below that at which bacterial growth will occur, to be used within a period of 48 hours. If a bacteriostatic agent is to be added to the final preparation with the pyrogen-free water as the vehicle, such preservative can be added to the latter and this stored under refrigeration for use for compounding purposes within a few days.

Containers for Parenteral Solutions

Glass containers are usually used. Clear glass is preferred, so that the contents can be readily examined. They must meet the requirements of the U. S. P. and N. F., these being the same in each compendium. The type of closure is very important, whether it be cotton-stoppered or muslin plugs, rubber stoppers or those made of other compositions. Glassware and closures must be of good quality and chemically clean. This requires thorough cleansing prior to sterilization or filling with the preparation and then sterilizing container and contents. The composition of glassware and procedures for washing the latter as well as closures were considered in detail earlier during this conference. Finally, it is important to be assured that the quality and the sterility of the contents are not impaired by improper packaging.

Sterilization Procedures

It is most important that one familiarize himself with the basic principles concerning the use of bacteriological filtration, steam sterilization (without as well as under pressure), dry heat sterilization and other methods employed for obtaining sterile preparations. Some of these were considered here today by others. The procedures are usually easy to perform, but it is important to constantly check the efficiency of the equipment and the techniques used.

I am delighted to record that due to the progress made through the efforts of the American Society of Hospital Pharmacists and its members, Hospital Pharmacists, more so than pharmacists in other divisions have concerned themselves with this, the most exacting of pharmaceutical practice—the manufacture of sterile products and preparations. However, only the surface has been scratched. Considerable more can be and should be done by the hospital pharmacist. Properly handled, this group can help place professional pharmacy in the position it rightly belongs. This will redound to your own interests, to that of pharmacy, and to the benefit of mankind.

Central Sterile Service Department

The Central Sterile Service Department or Division or the so-called "central supply" in most hospitals may have advantages in that operative procedures can be more easily and more effectively controlled, resulting in greater economy, efficiency and safety. However

the question arises, is this the place for the preparation of bulk and other parenterals, even if the latter are only such preparations as Injection Water, Sterile Salt Solution, Dextrose Injection, and the like. Most workers in these Central Sterile Service or Supply Departments or Divisions are non-professional or lay personnel, working supposedly under competent supervision. The word *competent* deserves serious considerations at times. I wonder how close has been the attention given by the hospital administration to the training and knowledge (general and specific for the duties embodied) possessed by such supervisors.

I don't think I need labor the point that drugs or preparations of the latter to be sterilized and in fact all parenterals should be prepared or manufactured under the supervision of a qualified pharmacist even in a Central Sterile Service or Supply Department or Division. The question also arises whether supervision of the Central Sterile Service Division or Department itself should not be placed under the direction of a qualified hospital pharmacist. I know that today many hospital administrators feel that a registered nurse should act as supervisor. The problem of selecting the proper personnel for supervising the operation of the Central Sterile Service Department cannot be discussed here and is not the subject assigned for consideration at this time. However, recognizing that the success of this department depends in great measure upon the qualifications and responsibilities of a most capable supervisor, I think that with little effort, data can be presented to point out that qualified pharmacists can act as responsible supervisors of the Central Sterile Supply or Service Departments or Divisions, so as to be assured that all duties are carried out in a most efficient manner. The assistant may be a nurse or at least there should be available an advisory group consisting of a qualified R. N., a member of the Surgical Staff, the Hospital Bacteriologist and even others.

Quality Control

When new equipment in the parenteral department or division is placed in operation and new formulations of sterile medicaments are prepared, it is most important that adequate methods of control testing are carried out, so as to be assured of the safety and the proper quality of the finished product. All testing can be done by a responsible outside laboratory. However, in many if not in most instances, the personnel in the pharmacy, in the clinical laboratory and in the

other available facilities in the institution, depending upon the size of the latter, can be found adequate for the performance of the necessary tests. Even with the latter, spot checking by a responsible outside laboratory is desirable. Whatever the quality control procedure, a report of the findings in writing should be sent to the administration office and a copy kept in the files of the pharmacist. Such quality testing program for new equipment, new techniques and new products will establish the effectiveness of the preparation to be made available and of the procedures employed. The kind of quality control program required to safeguard the production of parenterals, old and new, the significant tests to employ, and the frequency of performing these tests will depend upon the preparations being manufactured, the volume of the entire output and the conditions under which they are being produced.

Pyrogen Test

The test which most frequently is the concern of those handling parenterals is the Pyrogen Test. The nature of "true" pyrogens has not yet been fully established. Whether their structures vary and whether they are protein in origin or carbohydrate or complexes or combinations of these with or without lipids are not known. The one significant characteristic common to all so-called "pyrogens" is pyrogenicity, i.e., the production of fever or pyrexial reactions when given parenterally (and especially intravenously). It is apparent that the presence of pyrogens in parenterals reflects upon their quality and the fact that ingredients of the highest purity or scrupulous cleanliness or the most careful technique in preparation were not used. It was my pleasure to serve as a member of the U. S. P. Sterile Advisory Board, which for the first time in the existence of any official compendium introduced the biologic test for pyrogens. Even this test, which today is the most satisfactory as an indicator for the presence of pyrogens, does not require elaborate equipment and can readily be performed after some experience in most hospital laboratories. Furthermore, it is well to recognize that the Water for Injection or freshly distilled water is the one ingredient which is to be controlled more so than others to be assured that pyrogens are absent, as this is used as the vehicle in the vast majority of liquid parenterals. Actually pyrogen tests cannot be done on most marketed parenteral solutions, as the ingredients present would affect the animal when the latter was injected, so that a proper evaluation is not always

possible. It is only with preparations such as, Sodium Chloride Solution and Injection, Sodium Citrate Solution (Anticoagulant), A. C. D. Solution, Ringer's Injection, and Dextrose Injection, that testing the finished preparation for pyrogens by the biologic method is possible. However a pyrogen-free water should be employed at all times, when this is the designated vehicle.

Sterility Testing

Testing of the finished preparation for sterility should be practiced. This is not performed as frequently as it should be, if at all, on sterilized products processed in the Central Sterile Service Department. It is rare that the latter division carries along known positive contaminated controls to check the sterilization equipment and technique used. Certainly preparations for parenteral use should be checked for sterility. Methods are given in detail both in the N. F. and U. S. P. These procedures are not too difficult to perform, are not costly and can readily be performed by a trained pharmacist.

Parenterals in Hospitals

To assure safe parenteral preparations in a hospital, should they be purchased on the open market as commercially prepared products or should they be compounded and prepared in the institution needing them? What is the actual situation in most hospitals today? Does the hospital pharmacist prepare the sterile medicaments? How many hospital pharmacists prepare their own sterile multiple dose vials or sterile single dose injectables?

Many hospitals are reluctant to undertake a program of manufacturing parenterals. Is it a fear complex or have they had unsatisfactory past experiences? Do they think that it is too costly or that there is no saving economically? If there is, do the possible inherent hazards not warrant their manufacture?

In most hospitals, bulk parenterals are either purchased on the open market or prepared in the so-called Central Supply Room or Central Dressing Room (CDR) which I prefer to call Central Sterile Supply (or Service) Department (or Division). In some instances, both procedures are practiced.

Physicians, today, cannot prescribe for a mixture to be given parenterally and have this filled in a pharmacy (hospital or retail). They must prescribe the formulas commercially available and listed

in the catalogue of a manufacturer. Deviation from this formula means a special or private formula, which few manufacturers will attempt to prepare today. Even if they do, the cost is generally prohibitive.

Survey

In a survey made within the past two weeks under the auspices of Herbert Flack, President of the Philadelphia Hospital Pharmacists Association, a questionnaire concerning parenteral preparations was sent to the presidents of 43 chapters affiliated with the Society of American Hospital Pharmacists. To date, replies were received from 25 or approximately 60 per cent. In this group there were a total of 70 hospitals. Eight hospitals do not and 62 hospitals do manufacture parenteral preparations. Forty-five or 72 per cent of the latter (62) manufacture their parenterals under the supervision of a pharmacist; and to be exact 40 or 64 per cent manufacture parenteral solutions in the Pharmacy Division, and 5 or 8 per cent in the Central Sterile Service Division under the supervision of a pharmacist. Seventeen or approximately 28 per cent of these 62 hospitals manufacture parenteral solutions in the Central Sterile Service Division without any supervision by a pharmacist. Thirteen or approximately 18 per cent of the total number of 70 hospitals have a pharmacist in charge of the Central Sterile Service Division.

It would be desirable to extend this survey and obtain more definite data. For instance, I would venture the opinion that where parenterals are manufactured in a hospital, most of these are as bulk preparations; and they are more than likely such products as, Water for Injection, Saline Solutions, Dextrose Solutions, Sodium Citrate Solutions and the like. It would be desirable to learn this and other more exact information. From such data, committees on parenteral solutions, in each of the chapters of your Society under supervision of a National Committee could formulate plans best suited for your individual regions and/or for the entire membership.

The hospital pharmacist of the future must be qualified to prepare parenteral products. The extent to which this is to be practiced will depend upon the size of the individual institution and other factors briefly considered herein. It is even conceivable that in large metropolitan areas, two or more hospitals can coordinate their activities so that the manufacture of some or all parenterals is carried out under a joint arrangement.

Your Society can have working committees which, after pooling your individual information, can arrange to prepare suitable memoranda or instructions, giving details how to set-up such parenteral departments in hospitals, the procedures to employ in formulation, preparation and sterilization, the best controls to use and most suitable methods of testing. Finally, I can envision the time in the not too distant future when the American Society of Hospital Pharmacists will have its own members in a Board of Accreditation for functioning with others to accredit hospital pharmacies, including a Division for the manufacture of parenteral preparations, just as is done by other professional groups in accrediting hospitals.

The unique opportunities that the hospital pharmacist and this Society have in the display and practice of pharmacy at its best should be a challenge for all of you to serve professional pharmacy and pharmacy as a whole.

REFERENCES

(1) Gershenfeld, L., "Who is to Dispense Therapeutic Agents intended for Hypodermic and Intravenous Injection?" *The Pennsylvania Pharmacist 13:*101 (1931).

(2) Gershenfeld, L., Editorial: "Control of the Traffic in and the Labeling of Ampuls and Medicaments for Parenteral Administration," *Amer. Jour. Pharm. 105:*155 (1933).

(3) Committee Report: "A Report on Sterility of Ampule Preparations," *J. A. M. A. 103:*678 (1934).

(4) Gershenfeld, L., "Sterile Medicaments," *Amer. Jour. Pharm. 115:*5 (1943).

(5) Gershenfeld, L., "Bacteriostatic Agents in Parenteral Solutions," *Bull. Parent. Drug. Assoc. 7:*19 (1953).

(6) Martin and Cook, Parenteral Preparations, Chapter 28, "Remington's Practice of Pharmacy," 1956, The Mack Publishing Company, Easton, Pa.

DRUG INFORMATION SOURCES *

(Spain, Italy, Portugal)

SPAIN

Medicamenta; Guia Teorico-Practica para Farmaceuticos y Medicos. 5th ed., edited by Dr. Enrique Soler y Batlle. Barcelona, Editorial Labor, 1954. 2 vols. (1516, 1442 pp.) Approx. $25.00.

Volume 2 of this comprehensive two-volume reference work contains monographs on drugs arranged alphabetically by common or proprietary name. Monographs report alternate names, composition (sometimes with structural formula), description, identification and assay, a brief statement of therapeutic uses, pharmaceutical forms and dosage and precautions to be observed, if any. Manufacturers' names are not given. All drug names, including chemical names, are found in the general alphabetic index. Volume 1 consists of longer monographs on topics of interest in pharmacy, such as pharmaceutical preparations, chemical analysis, clinical chemistry, biologicals, enzymes, hormones, chemotherapy, pharmacology, and so forth. Publisher's address: Provenza 84-88, Barcelona.

Diccionario Espanol de Especialidades Farmaceuticas (DEDEF) 1956. San Sebastian, DEDEF, 1956. 1501 + 249 pp. 300.00 Ptas.

—. **Boletin Suplementario del DEDEF.** Published quarterly. Yearly subscription, 100.00 Ptas.

—. **Indices del DEDEF.** Publication expected in 1956 at approximately 250.00 Ptas.

DEDEF is an alphabetic list of specialties marketed in Spain with manufacturer, detailed composition, actions, indications, dosage, pack-

* A World List; compiled by the Pharmaceutical Section, Science-Technology Division, Special Libraries Association.

ing and price. A list of manufacturers with their addresses is included. A supplement containing additions and changes is bound with the main volume. The quarterly *Boletin Suplementario* provides information about new drugs and changes; issues are cumulative and the fourth quarterly issue contains information for the entire year. A separately published volume, the *Indices,* includes a listing of manufacturers with names of their products, an index to products listed in *DEDEF* by principal chemical constituent or class of compound and an index by therapeutic indications. Publisher's address: San Martin, 62, San Sebastian.

Formulario con sus Fundamentos de Terapeutica Clinica. 9th ed., by B. Lorenzo Velazquez. Madrid, Graficas Gonzalez, 1952. 1740 pp. 225 Ptas.

A physician's handbook and formulary containing information about drugs classified by broad systems of medicine, then by specific diseases. Specific drug information includes therapeutic applications, composition, method of administration and dosage. A special dosage table for adults and children is included for 470 medicinals. There is a general index to diseases and drugs. Specialties are mentioned in the text but not included in the general index. Publisher's address: Miguel Servet 15, Madrid.

ITALY

Medicamenta; Guida Teorico-Practica per Sanitari. 5th ed. Milan, Cooperativa Farmaceutica, 1949. 3 vols. (4011 pp.)

—. Supplement, 1956. Price for the complete work (4 vols.), Lit. 28.000.

The Italian *Medicamenta* is very similar to the Spanish *Medicamenta* but the special articles in Volume 1 are unsigned. The descriptions of drugs in Volumes 2 and 3 are somewhat more detailed. The source (i.e. author) of information is often identified but without specific bibliographic citation. There are a therapeutic index, a general index and an author index.

Repertorio Terapeutico 1956. 13th ed., edited by Dr. Riccardo Fumi. Milan, Aracne, 1956. 2 vols. (591, 434 pp.) Lit. 4500 in Italy; Lit. 7000 in U. S. A.

—. **Notiziario Farmaceutico,** ed. by R. Fumi. Yearly subscription, Lit. 1750.

Volume 2 is an alphabetic listing of products with indications, daily dosage, detailed composition and numbers referring to manufacturers' names (listed in Volume 1). A pharmacologic index to products described is included in Volume 2. In Volume 1 the same products are listed alphabetically with manufacturer's name and number, package sizes and price to public. The numbered list of manufacturers with their addresses and products and a list of wholesalers complete the volume. New products and changes are reported in the biweekly supplement, *Notiziario Farmaceutico.* Full revision occurs annually. Publisher's address: Via Cusani 5, Milan.

Specialità Farmaceutiche. Torino, **Minerva Medica,** 1956. Lit. 2000.

This annual supplement to the medical journal *Minerva Medica* has several sections, the most extensive being the *Dizionario,* an abridged list of specialty drugs giving for each its manufacturer and address, composition, actions, indications, forms supplied and price, and dosage. A more extensive list of specialties with brief indication of manufacturer and action is also included, as well as a list of pharmaceutical firms with their addresses and products and a therapeutic index to specialties. Publisher's address: Corso Bramante 83-85, Torino.

Terapia Galenica e Specialità Medicinali. 3d ed., 1952-1953, by C. Bussolati and R. Fumi. Milan, Aracne, 1952. 1159 pp. Lit. 2500.

One section lists pharmaceutical specialties and gives for each its manufacturer, therapeutic indications, composition, method of administration and dosage. Another section lists broad classes of drugs according to therapeutic indications (i.e., sulfonamides, calcium, iron preparations) and gives names of specialties and non-proprietary drugs belonging to these classes. A list of of pharmaceutical manufacturers is also included. Publisher's address: Via Cusani 5, Milan.

Dizionario delle Materie Prime Terapeutiche 1956-1957, edited by R. Fumi. Milan, Aracne. Lit. 4000.

The *Dizionario* lists products employed for the preparation of drugs marketed in Italy and sources of these products. The drugs are those indexed in *Repertorio Terapeutico.* Publisher's address: Via Cusani 5, Milan.

L'Informatore Farmaceutico Italiano 1957, edited by Dr. Luis Marini. Milan, Organizzazione Editoriale Medico Farmaceutica, 1956. 939 pp. Lit. 5000.

—. **Quindicinale Italiano d'Informazione Medico-Farmaceutica.** Yearly subscription, Lit. 2000.

Part I of *L'Informatore* is an alphabetic price list of drugs sold in Italy with name of manufacturer or distributor, brief statement of composition, packing and wholesale and retail prices. Part II gives the same information for veterinary drugs and Part III for household remedies, dentifrices, cosmetics, etc. A list of manufacturers with their Italian addresses and names of their products, a list of home addresses of foreign firms and list of wholesalers complete the text. The biweekly supplement *Quindicinale Italiano d'Informazione* announces new drugs and changes. Publisher's address: Via Edolo 40, Milan.

Repertorio dell' Industria Farmaceutica Italiana, 1954-1955. Milan, Casa Editrice Edizione Techniche. 900 pp. Lit. 3500.

Alphabetic and geographic lists of Italian pharmaceutical firms with their products and lists of products with their manufacturers. A new edition has been announced for May 1957. Publisher's address: Via Bazzini 20, Milan.

Repertorio Veterinaria 1955, ed. by R. Fumi. Milan, Aracne, 1955. 232 pp. Lit. 1200.

A list of veterinary drugs with composition, indications, dosage and manufacturer. New products and changes are reported in *Notiziario Farmaceutico* (supplement also to *Repertorio Terapeutico*). Publisher's address: Via Cusani 5, Milan.

PORTUGAL

Simposium Terapeutico; Enciclopedia de Especialidades Farmaceuticas. 1st edition. Lisbon, Editorial Ultramar, 1956. 356 pp. plus unnumbered pages.

The principal sections of this compilation are as follows: Part I, An alphabetic list of specialties sold in Portugal with name of manufacturer and name of distributor in Portugal. Part II, Alphabetic list of specialties with summary of information about their composition, indications, dosage and pharmaceutical forms. Part III, An index classified by therapeutic indications with names of specialties used in the conditions named. Part IV, A list of Portuguese distributors and representatives of foreign firms and their products. The publisher is to be commended for the attractive format and printing of the *Simposium,* which made its first appearance in 1956.

Anuario Medico de Portugal; Continental, Insular e Ultramarino. Lisbon, Adelino dos Santos. Annual.

Contains a section "Especialidades Farmaceuticas", a list of specialties with name of manufacturer, composition, indications, dosage and forms supplied. Lists of manufacturers and Portuguese representatives of foreign firms with their products are also included. Publisher's address: Rua de S. Bernardo 84, Lisbon.

The Committee on Drug Information Sources has the following members:

Anne McCann, *Chairman;* Elizabeth Boykin, Harold Oatfield, James L. Olsen, Jr., Maxine Painter, Clara Robeson, Walter Southern, Irene Strieby and Charlotte Studer.

A limited number of reprints are available for distribution by the Committee at 30¢ each. Requests should be sent to the Chairman at the Library, Squibb Institute for Medical Research, New Brunswick, N. J.

Regular distribution will not be undertaken by the Section. Individuals and libraries wishing to ensure continued receipt of "Drug Information Sources" may do so by entering subscriptions to *American Journal of Pharmacy.*

Correspondence about "Drug Information Sources" should be directed to the Chairman at the Library, Squibb Institute for Medical Research, New Brunswick, N. J.

THE PROBLEM OF ATHEROSCLEROSIS

By L. F. Tice

Atherosclerosis is the principal cause of the many cardiovascular diseases. For this reason, it is of tremendous importance. So far, no clear understanding of its causes is available but much is known about it and the factors that predispose one to this condition.

ATHEROSCLEROSIS, since it is the principal form or cause of arteriosclerosis, is often considered as a synonym for this term. Arteriosclerosis is a generic name for a number of pathologic conditions affecting the intima or the media of arteries and leading to a thickening and hardening with a loss of elasticity of the arterial wall.

Atherosclerosis is that specific form of arteriosclerosis characterized by areas of intimal thickening due to accumulations of lipids and often followed by calcification. The term atherosclerosis is from the Greek *athere* meaning porridge and was so named because of the mushy appearance of these deposits.

Early Appearance

The earliest appearance of these lesions are the fatty streaks seen in the thoracic aorta of children. In later life, they are more severe in the abdominal aorta and, if they extend into the media, the wall may be weakened leading to an aneurysm.

Microscopically, atheromata consist of fat droplets, foam cells, fibrous proliferation, and necrotic debris containing cholesterol crystals. Calcification may also be present. As these plaques grow, they reduce the lumen of the artery, their centers may rupture releasing necrotic material into the blood stream, and a thrombus forms over the plaque. Stenosis or occlusion by such thrombus formation is common.

Cardiac and Cerebral Effects

Since in later life atherosclerosis has a predilection for the coronary and cerebral arteries, serious results can ensue leading to marked physical impairment and even sudden death. If a coronary artery is involved, occlusion by thrombus formation and subsequent myocardial infarction is common. The extent of this damage deter-

mines whether thes heart still can function sufficiently to maintain life or not. In the early stages of coronary atherosclerosis, the diminished blood supply often causes anginal attacks as the coronary muscle anoxia produces spasm. Such patients usually later suffer an occlusion. The involvement of the cerebral arteries leads to forgetfulness, confusion, and changes in personality produced by poor cerebral circulation. A cerebrovascular accident often takes place, particularly if the patient also has high blood pressure.

Diabetics are particularly prone to atherosclerosis of the leg arteries. As the lumen is reduced, intermittent claudication results and poor circulation may cause gangrenous ulcers.

Etiologic Factors

At one time, it was generally believed that atherosclerosis was a natural consequence of aging but this seems not to be true. At present, it is believed to be a metabolic disorder. Young people sometime show marked atherosclerotic lesions while some people of 70 or 80 years of age may be almost without the condition. Many factors are believed to influence its development including heredity, diet, sex, and others.

The precise role of heredity as a factor is not clear. Whether a predisposition to the disease is carried by the genes or whether certain characteristics leading to dietary patterns, etc. are transmitted genetically is not established. There does seem to be some familial tendency to the disease.

In recent years, it has been observed that atherosclerosis is not as common in young females as in males the same age. After the menopause, this sex difference in incidence seems to diminish. This has led investigators to relate a high blood estrogen level with a low incidence of atherosclerosis. It is also one of the several reasons proposed for the inclusion of a small amount of some estrogen in geriatric vitamin-mineral supplement capsules. When so used, it is believed best to combine the estrogen with an androgenic steroid to offset unfavorable side effects as well as to contribute an anabolic action.

Diet

A close relationship seems to exist in the nature of diet and the incidence of the disease. The dietary factor of primary importance is the amount and kind of fat in the diet.

Keys and Brock studied three groups of South Africans having different dietary levels and related diet, blood cholesterol levels, and the incidence of myocardial infarction. They found that those of European ethnic origin had the highest fat consumption, the highest blood cholesterol values, and the highest incidence of infarction.

Bantus who consummed little fat had a much lower blood cholesterol and myocardial infarction was rare. Negroes who had adopted some of the European dietary habits were intermediate. Europeans who during World War II were deprived of a high fat diet experienced a sharp drop in coronary heart disease.

Some populations consume fats in relatively large amounts without a high incidence of atherosclerosis or its implications. Such is the case with Southern European people and the Eskimo. It is currently believed that this is because the fats they consume are either vegetable fats or fish and seal oils. Such fats are richer in unsaturated fatty acids. The fats of land animals are much more highly saturated and, as such, seem to be more harmful in contributing to atherosclerosis.

Hypercholesterolemia

The lipids of the blood consist of three important classes: (a) the true fats; i.e., the triglycerides; (b) the phospholipids, substances such as lecithin; and (c) cholesterol and its esters. Fatty acids are a constituent of all three except in the case of free cholesterol.

Serum lipids exist as a lipid-protein complex or lipoproteins. These giant molecules or particles have been classified by Cohn and his co-workers as alpha-lipoprotein and beta-lipoprotein, the latter having a molecular weight of about 1,000,000 and the former, about 200,000.

Attempts to relate blood cholesterol levels with the development of atherosclerosis have not always shown a correlation. Some persons with hypercholesterolemia show no evidence of atheromata while others with normal values may have marked atherosclerosis.

Gofman and his associates have made studies of blood lipoproteins using the ultracentrifuge. The beta-lipoprotein fraction was first separated from the alpha fraction by suspending in a salt solution of low density followed by centrifuging. The beta fraction floated to the surface since it is composed of molecules having a density less than that of the medium. The rate at which each component of this fraction floated to the surface was expressed in Svedberg flotation units (Sf).

This unit is equal to 10^{-13} cm./sec./dyne/g. A speed of 52,000 r.p.m. was used to produce this flotation.

Gofman demonstrated a number of lipoprotein fractions ranging from those of Sf = 70 and over to the smallest, with Sf = 2-10. Those of the highest Sf values contain the highest amount of lipid.

Gofman made some correlation between a high ratio of Sf 10-20 lipoprotein and atherosclerosis in humans. He also showed that feeding rabbits on a high cholesterol and fat diet increased the beta-lipoprotein content of their serum. Cholesterol in amounts of 3 Gm. daily caused the appearance of Sf 10-30 giant lipoprotein molecules and atheromatous lesions in the arteries.

Gofman, in a long series of human subjects, showed a correlation of Sf 10-20 lipoproteins and the sex preference for atherosclerosis in young adults, a correlation with myocardial infarction and the effect of a low fat diet in reducing the amount of this Sf 10-20 fraction.

Early Detection

While blood cholesterol values are of some significance, they do not provide a criterion for the detection of developing atherosclerosis. Ultracentrifuge studies for the Sf 10-20 lipoproteins, while more meaningful, are not practical for routine diagnosis.

Some early symptoms are prematurely gray hair, poor growth and roughness of the toe nails and finger nails, loss of skin texture, and wasting of leg muscles. An examination of mental status, eye grounds, and palpation of certain arteries may also give some evidence. Unfortunately, many patients are symptom-free until angina or an occlusion results.

Some recent experimental work by Rinzler has led to a test using ergonovine maleate. In subjects with coronary atherosclerosis, the vasoconstriction causes a response in the electrocardiogram seen as a depression of the S/T segment. This test, known as the ergonovine stress test, may prove of great diagnostic value in detecting atherosclerosis in symptom-free patients.

Therapy and Prophylaxis

A cholesterol free diet seems a poor approach in prophylaxis since it has been shown that the body can synthesize cholesterol from such simple substances as acetates.

A low fat diet and one poor in saturated (animal) glycerides is believed useful in prophylaxis. Excess body weight predisposes one to atherosclerosis so that maintaining normal or even below average weight is desirable. The use of tobacco is undesirable since it is known to cause vasoconstriction in both the coronary vessels and the extremities. Emotional stress and tension are contributing factors and should be corrected if possible.

The use of the so-called lipotropic factors including choline, methionine and inositol has not produced any marked results. These have been tried clinically in view of their value in preventing fatty deposits and degenerative changes in the liver. Since no drug is known which will reverse atherosclerotic changes, the best that one can hope to do is to arrest the progress of the disease. Heparin has been shown to have a lipid clearing effect in the blood, reducing the level of Sf 10-20 lipoprotein molecules. It is difficult, however, to outline therapy using heparin because of its hazards and its cost. The possible role of a heparin deficiency as an etiologic agent has been suggested.

Sitosterol

During the last year, some clinical reports were released indicating that the oral administration of a suspension of a mixture of beta-sitosterol and its dihydro derivative might be useful in reducing hypercholesterolemia. It is presumed to act by interfering with the absorption of dietary cholesterol and also that formed within the body. The latter (endogenous) is secreted via the bile into the small intestine from which it is normally resorbed. The presence of the sitosterol interferes with this mechanism.

Sitosterol is given in a dose of 9-36 Gm. daily in divided doses after meals. It is a plant sterol differing from cholesterol only in the presence of an ethyl group on the aliphatic side chain. It is available as a 20 per cent flavored suspension as Cytellin (Lilly). The precise value of this therapy cannot yet be estimated.

Should the time come when specific therapeutic measures are found to treat atherosclerosis, life-expectancy of all adults will grow by several years and that of males in high economic status, most of all.

SELECTED ABSTRACTS

Polyacrylic Resin in the Treatment of Constipation. Grossman, A. J., Batterman, R. C., and Leifer, P. *J. Am. Geriat. Soc.* 5:187 (1957). A new synthetic polyacrylic resin of the polycarboxylic type with hydrogen occupying the cation exchange position was used in the treatment of constipation in 37 bedridden patients and 37 ambulatory patients. This new resin was selected because of its high water-binding capacity. It was found that it could bind 70-105 ml. of water per Gram when dispersed in distilled water and 70-94 ml. per Gram when dispersed in artificial intestinal juice. This is several times greater than psyllium gums, agar gums, and methyl cellulose derivatives. The ionic exchange capacity for sodium was found to be only from 1 to 3 per cent. Because of its high molecular weight, the resin was not absorbed from the gastro-intesinal tract.

Of the 31 bedridden patients receiving 4 Gm. of the resin a day, 71 per cent showed improvement. The rest of the bedridden patients had received 3 Gm. or less a day and had showed less improvement. Improvement was noted in most of the patients within 3 to 7 days. The first indications of improvement were an increased ease of removal of fecal material by enema or manipulation. Gradually, spontaneous bowel movements occurred with increasing regularity.

Among the ambulatory patients, a dose of 450 mg. 3 or 4 times a day was found to be unsatisfactory. However, when the dosage was increased to 0.9 to 1.0 Gm. 3 or 4 times a day, effective control of bowel function was established in 77 per cent of 31 patients. Once daily bowel movements were established, it was found to be possible to decrease the dosage in 13 patients and in 7 patients to eventually discontinue the resin and still maintain normal bowel function without laxatives.

Signs of intolerance of the resin were negligible. Two of the ambulatory patients had flatulence but none of the bedridden patients had any signs of gastro-intestinal disturbance. Edema was not observed in any patient. None of the patients complained of fullness of the stomach. The resin apparently did not interfere with the absorption of other drugs required.

The Action of Antibiotics on Strains of Pseudomonas Aeruginosa and Proteus Vulgaris. Nordbeck, S. *Arzneimittel-Forschung 7:*179 (1957). The resistance of strains of *Pseudomonas aeruginosa* and *Proteus vulgaris* is of considerable interest because of the severe infections which sometimes develop as a result of the invasion of these organisms. The author conducted a series of *in vitro* tests on the resistance of 15 strains of *Pseudomonas aeruginosa* and 24 strains of *Proteus vulgaris* to 11 antibiotics. The antibiotics tested were penicillin, dihydrostreptomycin, tetracycline, oxytetracycline, neomycin, viomycin, polymyxin B, bacitracin, erythromycin and a combination of xanthocillin and tyrothricin.

As would be expected, the author found that some strains showed appreciable difference in sensitivity to some of the antibiotics from that of other strains. The strains of *Pseudomonas* were consistent in their resistence to penicillin, viomycin and bacitracin. The antibiotics most effective against *Pseudomonas* were polymyxin B and the combination xanthocillin-tyrothricin. These antibiotics were consistently effective at low concentration levels against all of the strains tested.

Against *Proteus vulgaris,* oxytetracycline, viomycin, polymyxin B, and bacitracin were particularly ineffective. The most effective antibiotics against this organism were penicillin, neomycin and the combination xanthocillin-tyrothricin in the ratio 1:1. However, two strains of *Proteus* were resistant to penicillin. These same strains were not resistant, however, to neomycin or the combination of xanthocillin-tyrothricin.

The Relationship Between Age and the Level of Vitamin B_{12} in the Serum. Gaffney, G. W., Horonick, A., Okuda, K., Meier, P., Chow, B. F., and Shock, N. W. *J. Gerontol. 12:*32 (1957). The serum levels of vitamin B_{12} were obtained in the fasting state from 528 apparently healthy individuals between the ages of 12 and 94. The patients were obtained from four sources and grouped accordingly. One group was from a public home for the aged, one from a penal institution, one from a sampling of a city population, and a fourth from a private home for aged.

The reliability of the test methods were checked by assaying portions of pooled sera preserved in the frozen state during the interval in which analyses were performed. No systematic trend was evident. Recovery by the microbiological method was checked against radio-

activity assays of cobalt-labelled vitamin B_{12} added to pooled sera. Good comparisons were obtained.

Statistical evaluation of the results showed that the regression of serum vitamin B_{12} levels found to occur with increasing age was highly significant. A comparison of the 20 to 49 year age group with the 50 to 94 year age group revealed that the percentage of those having serum levels of less than 100 $\mu\gamma$/ml. in the younger group was 0.83 as compared with 18.2 in the older group.

The authors found that there was excellent agreement among the regression lines of the four groups. This agreement, when there was such a wide difference in the backgrounds and in the living conditions of these groups, suggested that the regression observed had no significant correlation with backgrounds and living conditions. The authors suggested that, if dietary conditions per se played a significant role in the age-related decrease in serum vitamin levels, they did so as a consequence of some age-related alteration in the selections of foods by the subjects themselves.

Cervico-Vaginal Infections Treated With Hexetidine. Hoefer, W. H. V., Bailey, F. A., and Farley, W. W. *Antibiot. Med. & Clin. Ther. 4*:31 (1957). A new synthetic compound named hexetidine (bis-1,3-beta-ethylhexyl-5-methyl-5-amino hexahydropyrimidine) was found to have wide antibacterial and antifungal activity. It was employed by the authors in the treatment of 327 patients with vaginal and cervical infections of bacterial and fungal origin. It has also been used on a variety of other types of eye, ear, nose, throat, and skin infections but, these were not reported in this article.

The compound was applied topically in the form of a 0.5 per cent colloidal dispersion in polyvinylpyrrolidone or in a gel containing 0.1 per cent of the hexetidine at a pH of 4.2. Two approaches were employed in treatment. In one, only the solution was applied during an office treatment using cotton swabs and tampons with about 10 minutes of contact time. In the other, in addition to the office treatment, the patient was given a tube of the gel and instructed to apply an applicator full three times a week high in the vagina at the time of retiring. The office treatment was repeated every week or two.

The authors reported that the infection was completely cleared in 65.4 per cent of the patients and improved in 28.2 per cent. Only 6.4 per cent of the patients showed no improvement. Among those

showing improvement, clinical symptoms generally disappeared after 2 to 3 treatments. This varied somewhat depending upon the severity and chronicity of infection. A few patients required a second series of treatments. The criterion of cure was based upon smears and the disappearance of clinical signs of infection.

The authors indicated that there were no instances of sensitization, irritation, or systemic toxicity observed which were attributable to the drug.

The Effect of Prednisone and Prednisolone in Promoting Infections. Foley, E. J., Morgan, W. A., and Greco, G. *Antibiot. and Chemother. 7*:65 (1957). Experimental infections with *Streptococcus* strains in mice were studied with regard to the effect of prednisone, prednisolone, cortisone, and hydrocortisone in promoting the infection when treated with chlortetracycline. The authors indicated that the data given were representative of many experiments performed with other bacterial infections treated with other antibiotics.

The data given showed that prednisone and prednisolone, like cortisone and hydrocortisone, interfered with the defense mechanisms of the body. That is, when a significant percentage of control animals treated with the antibiotic died, treatment with the steroids further increased the number of deaths. However, there was no indication that prednisone or prednisolone were more active on a weight basis that cortisone or hydrocortisone in interfering with the chemotherapeutic effect of chlortetracycline. However, this effect was not observed with any of the four steroids unless massive doses were given. For example, repeated doses of 5 mg. per Kg. of body weight in the infected mice (approximately 10 times the usual higher range of dosage in man) showed no untoward effect. On the other hand, doses of 40 mg. per Kg. in the infected mice markedly reduced the effectiveness of chlortetracycline in preventing death.

The authors concluded, therefore, that prednisone, prednisolone, cortisone and hydrocortisone should be used with caution when infection is suspected or established. However, evidence would seem to support the fact that the danger of promoting infections by these steroids has been over emphasized through failure to take into consideration the massive doses of the corticoids required to demonstrate this effect in animals.

Expanding Meti-steroid benefits to an ever-broadening field of therapy

METICORTEN® Tablets

METICORTELONE® Tablets

METICORTELONE Acetate Aqueous Suspension

SIGMAGEN* Tablets

METI-DERM* Cream

METI-DERM Ointment with Neomycin

METIMYD* Ophthalmic Suspension

METIMYD Ointment with Neomycin

METRETON* Tablets

METRETON Nasal Spray

Schering

*TM

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

Former Editors of the Journal have been: Daniel B. Smith, 1825-1828; Benjamin Ellis, 1829-1831; Robert E. Griffith, 1831-1836; Joseph Carson, 1836-1850; William Procter, Jr., 1850-1871; John M. Maisch, 1871-1893; Henry Trimble, 1893-1898; Henry Kraemer, 1898-1917; George M. Beringer, 1917-1921, and Ivor Griffith, 1921-1941.

Established and maintained as a record of the progress of pharmacy and the allied sciences, the Journal's contents and policies are governed by an Editor and a Committee on Publications elected by the members of the College.

Manuscripts should be sent to the Editor, who does not assume any responsibility in connection with the views or investigations of contributors of accepted manuscripts, other than to exercise general care in selection.

Contributors are allowed a reasonable number of copies of this Journal, free of charge, if applied for when the proof is returned.

Reprints, if desired, should be ordered when the proof is returned. The table below shows the *approximate* cost of reprints, the make-up of the pages to be identically the same as in the Journal. The actual cost may vary from the figures given, and will depend upon the amount of presswork, paper, binding, and other factors. Reprints containing half-tones may be expected to cost somewhat more than the rates given.

	2 pp.	4 pp.	8 pp.	16 pp.	Covers with Titles	
50 copies.....	$ 4.50	$10.00	$16.25	$27.50	50 copies.....	$ 7.50
100 "	7.50	13.75	21.25	40.00	100 "	12.50
250 "	10.00	17.50	27.50	53.75	250 "	17.50
500 "	15.00	25.00	35.00	68.75	500 "	26.25

You know those rare days when *everything* checks? Air smells good. Food tastes terrific. Even the old face looks good in the mirror. *Today* can be that kind of day. Just do two things. Call your doctor for a thorough medical checkup for cancer. Then write out a check—a nice fat one — to the American Cancer Society, and send it to "Cancer" in care of your local Post Office.

AMERICAN CANCER SOCIETY